DETAILED ACTION

Response to Amendment

Claims 1, 3, 6 and 22 have been amended, claim 28 has been canceled and new claims 41-49 have been added as requested in the amendment filed on 02 July 2008. Claims 1, 4, 5 and 7 have been amended, and claim 6 has been canceled as requested in the amendment filed on 28 July 2008. Further, the response filed on 16 January 2009 has been received and entered in full. No claim amendments were submitted in the response filed on 16 January 2009.

As stated in the notice of non-responsive amendment dated 14 October 2008, applicants have elected one antibody species, i.e. the MSR-7 antibody, from the species set forth in the restriction requirement dated 05 June 2007. According to the specification (e.g. Figure 4 and sequence listing), the 6 CDR sequences for the elected MSR-7 antibody are L-CDR1=SEQ ID NO: 143, L-CDR2=SEQ ID NO: 144, L-CDR3=SEQ ID NO: 18, H-CDR1=SEQ ID NO: 146, H-CDR2=SEQ ID NO: 147 and H-CDR3=SEQ ID NO: 24. Thus, the amendment dated 02 July 2008 presented claims that were considered non-elected because claim 1 and dependent claims recite different sequences from those set forth above. In the response filed on 16 January 2009 (see pp.9-11), applicants assert that the amended claims still encompass the CDR sequences of MSR-7. Applicants assert that the sequence listing contains redundant SEQ ID NOs for the same sequence and assert that L-CDR1=SEQ ID NO: 143 is the same as SEQ ID NO: 96, L-CDR2=SEQ ID NO: 144 is the same as SEQ ID NO: 97, H-

CDR1=SEQ ID NO: 146 is the same as SEQ ID NO: 99 and H-CDR2=SEQ ID NO: 147 is the same as SEQ ID NO: 100. Applicants also assert that claim 41 was presented because MSR7.9.H.7 is an affinity matured version of MSR-7, having substantial structural identity to MSR-7. Applicants assert that four of the six CDR sequences of MSR7.9.H.7 (L-CDR1, L-CDR2, H-CDR1, and H-CDR3) are identical to that of MSR-7 antibody, which has already been searched. Applicants request that claims 41-49, which list the CDRs of MSR7.9.H.7, be considered because they closely correspond to the MSR-7, whose CDR sequences have already been searched and examined.

Applicants' arguments have been fully considered and are found persuasive. The examiner agrees that claim 1 and dependent claims still encompass the elected antibody of MSR-7 (note: L-CDR1=SEQ ID NO: 96, L-CDR2=SEQ ID NO: 97, L-CDR3=18, H-CDR1=SEQ ID NO: 99, H-CDR2=SEQ ID NO: 100, and H-CDR3=SEQ ID NO: 24). The two additional sequences of MSR7.9.H.7 recited by claim 41 and dependent claims, i.e. SEQ ID NO: 95 and SEQ ID NO: 93 will also be examined.

Claims 1-5, 7-9, 11-16, 22, 29, 30 and 41-49 are now pending and under consideration to the extent that the claims encompass the 8 CDR sequences set forth above (for search purposes).

Information Disclosure Statement

A signed and initialed copy of the IDS paper filed on 21 January 2009 is enclosed in this action. One reference was crossed out because it was not

furnished in English and there was no statement of the relevance of the reference in compliance with the requirements of 37 CFR1.98 (a)(3). See MPEP 609. Although applicants have stated they have provided a concise explanation of the relevance of the document, the examiner is unable to find any such explanation.

Objections/Rejections Withdrawn

The Sequence Rules Requirement set forth in the previous office action dated 28 January 2008 is withdrawn in response to submission of the amended sequence listing and the amendments to the specification.

The rejection of claims 1-3, 8, 9, 15, 16, 29 and 30 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,955,317 to Suzuki et al. is withdrawn in response to the amendment to the claims to recite 6 specific CDR sequences, which are not disclosed by Suzuki et al.

The rejection of claims 11-14 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,955,317 to Suzuki et al. in view of Knappik et al. is withdrawn in response to the amendment to the claims to recite 6 specific CDR sequences, which are not disclosed by Suzuki et al. or Knappik et al.

The scope of enablement rejection of claims 4 and 5 under 35 U.S.C. 112, first paragraph, is withdrawn in response to the amendment to the claims to recite 6 specific CDR sequences.

The scope of enablement rejection of claim 6 under 35 U.S.C. 112, first paragraph, is withdrawn as moot in response to the cancellation of said claim.

The rejection of claim 22 under 35 U.S.C. 112, second paragraph, is withdrawn in response to the amendment to the claim that deleted dependency on canceled claims.

The rejection of claim 28 under 35 U.S.C. 112, second paragraph, is withdrawn as moot in response to the cancellation of said claim.

New and remaining issues are set forth below.

Claim Objections

Claims 1-5, 7-9, 11-16, 22, 29 and 30 are objected to because of the following informalities: The claims contain non-elected subject matter (SEQ ID NOs other than L-CDR1=SEQ ID NO: 96, L-CDR2=SEQ ID NO: 97, L-CDR3=18, H-CDR1=SEQ ID NO: 99, H-CDR2=SEQ ID NO: 100, and H-CDR3=SEQ ID NO: 24). Appropriate correction is required.

Claim 45 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 43. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). SEQ ID NO: 89 (recited by claim 43) is identical to SEQ ID NO: 425 (recited by claim 45). Therefore, there are no embodiments within the scope of either claim 43 or 45 which are not encompassed by the other.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7-9, 11-16, 22, 29 and 30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims are broadly drawn to antibodies, which comprise a very large number of different combinations of claimed CDR sequences or fragments thereof

The specification discloses only particular combinations of the 6 CDR sequences will result in antibodies that bind to antigen as claimed (see e.g. Table 1, pp.64-68). The specification does not describe antibodies that comprise random combinations of the CDR sequences encompassed by the claims (and fragments thereof), i.e. the examiner is unable to find any support in the disclosure as-filed for the claimed antibodies that comprise random combinations of the CDR sequences and fragments thereof. Applicants are required to cancel the new matter in the response to this Office action. Alternatively, applicants are invited to identify sufficient written support in the original specification for the "limitations" indicated above.

Claims 1-5, 7, 8, 9, 11-16, 22, 29 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antibodies that comprise 6 CDRs, wherein: L-CDR1 comprises SEQ ID NO: 96, L-CDR2 comprises SEQ ID NO: 97, L-CDR3 comprises SEQ ID NO: 18, H-CDR1 comprises SEQ ID NO: 99, H-CDR2 comprises SEQ ID NO: 100 and H-CDR3 comprises SEQ ID NO: 24 (i.e. the 6 CDRs of the elected MSR-7 antibody) or that comprise the particular combinations of antibodies disclosed in Table 1 of the specification, does not reasonably provide enablement for an antibodies that contain any other combination of the CDRs recited by independent claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

The claims are broadly drawn to antibodies or fragments thereof, which comprise a very large number of different combinations of claimed CDR sequences.

The specification discloses only particular combinations of the 6 CDR sequences will result in antibodies that bind to antigen as claimed (see Table 1, pp.64-68). The specification does not enable antibodies that comprise random combinations of the CDR sequences encompassed by the claims (and fragments thereof), i.e. the specification does not teach that the artisan can pick and choose different combinations of the claimed CDRs and still produce an antibody that binds antigen as claimed. Further, the specification does not teach that any random combination of the CDRs as claimed will also comprise the sequences encompassed by claims 4 and 5. Thus, the specification does not enable to the full scope of the claims.

As stated previously, it is well established in the art that the formation of an intact antigen-binding site of all antibodies requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, citation U on PTO-892 dated 28 January 2008, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of

heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (citation V on PTO-892 dated 28 January 2008, page 1979). The Rudikoff reference teaches that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that the antibodies and fragments thereof as defined by the claims, which may contain less than the full complement of CDRs from the heavy and light chain variable regions have the required binding function. Applicants have provided insufficient evidence or nexus that would lead the skilled artisan to predict the ability of producing an antibody and fragments thereof containing random combinations of the CDRs encompassed by the claims, thus resulting in an antibody that retains the antigen specificity currently claimed. However, as stated previously, the claim language also reads on small amino acid sequences, which are incomplete regions of the variable region of the antibody and which do not necessarily bind antigen, i.e. the "fragment thereof" of claim 1 and dependent claims does not require antigen binding. One of skill in the art would neither expect nor predict the appropriate functioning of the antibodies as broadly as is claimed.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such

guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

Therefore, in view of the lack of guidance in the specification and in view of the discussion above, undue experimentation would indeed be required to use the invention commensurate with the scope of the claims.

Claim 7 stands rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 7 is directed to the antibody molecule of claim 1, wherein said antibody is selected from the group consisting of MSR-7 and an affinity-matured version of MSR-7. The invention employs novel biological materials, specifically the MSR-7 antibodies. Since the biological materials are essential to the claimed invention they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public. If the biological materials are not so obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the biological materials. The specification does not disclose a repeatable process to obtain the specific biological materials and it is not apparent if the biological materials are readily available to the public. It

appears that applicants have not deposited the biological materials, and a deposit at a recognized depository may be made for enablement purposes.

In the reply filed on 02 July 2008, applicants assert that the specification sets forth the amino acid sequences (and encoding nucleic acid sequences) of the variable regions of MSR-3, MSR-7, and MSR-8 antibodies, e.g. at p.14, lines 16-20 and lines 24-27. Applicants assert that with the disclosure of both the amino acid and the encoding nucleic acid sequences, a person skilled in the art may readily construct the MSR-3, MSR-7, and MSR-8 antibody molecules. Furthermore, applicants assert that the six CDRs of affinity-matured versions of the antibodies are disclosed, for example, in Table 1. Thus, applicants assert that affinity-matured versions may also be readily reproduced. Accordingly, applicants assert that the specification disclose repeatable processes for obtaining the biological material as set forth in claim 7.

Applicants' arguments have been fully considered and are not found persuasive. Claim 7 clearly encompasses the actual monoclonal antibodies, not just any antibody comprising the recited sequences. Antibodies are defined not only by their small antigen-binding regions, but also by the remainder of their structure. The process of producing monoclonal antibodies is unpredictable; even when a small antigen is used multiple different monoclonal antibodies can be produced. See for example Kuby (1997. Immunology, Third Edition, pp.131-134), which teaches the process by which monoclonals are produced. See also Alberts et al. (1994. Molecular Biology of the Cell, 3rd Edition, pp.1216-1220), which teaches the three-dimensional structure of antibodies is complex. Note

particularly the large models on pp. 1219-1220 which indicate that the antibody molecules are comprised of hundreds of amino acids. The structure of a large protein such as an antibody is dependent not just on the antigen-binding region, but on the totality of the interactions of the hundreds of amino acid residues. Furthermore, Alberts teaches that the constant domains of the antibodies determine certain properties of the antibodies (see for example p.1217, final paragraph).

The specification fails to disclose the complete sequence and structure of the MSR-7 antibody and affinity-matured versions of the MSR-7 antibody, which is encompassed by claim 7. The art recognizes that specifying the sequence of the variable region alone is not sufficient to determine the entire structure of an antibody, and that making monoclonals is an unpredictable process. Monoclonal antibodies are so unique that a skilled artisan cannot simply construct one, the actual hybridoma which secretes the antibody must be present in order to make it. Thus deposit of said hybridoma is required for compliance with § 112, first paragraph. MPEP § 2404.02 recognizes that when undue experimentation would be required for an artisan to make a biological product, deposit can be required. The examiner has concluded that in order to make the actual antibody MSR-7 and affinity-matured versions thereof, the hybridoma is required.

Elements required for practicing a claimed invention must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. When biological material is required to practice an invention, and if it is not so obtainable or available, the enablement requirements of 35 USC

§112, first paragraph, may be satisfied by a deposit of the material. See 37 CFR 1.802.

The specification lacks sufficient deposit information for the monoclonal antibody MSR-7. Because this monoclonal antibody is unknown, and therefore, publicly not available and cannot be reproducibly isolated from nature without undue experimentation, a suitable deposit for patent purposes is required.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or Declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be **irrevocably removed** upon the granting of a patent;

(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803-1.809 for additional explanation of these requirements.

For the reasons above, it would not be possible for the skilled artisan to make the antibodies recited in claim 7. Therefore the rejection is maintained.

Conclusion

Allowable Subject Matter

Claims 41-43 and 46-49 are allowable. It is noted that the antibody of claims 41-49 is is not a naturally occurring product. Said antibody is a recombinant antibody, which is not naturally occurring and must be produced by one skilled in the art.

Claims 1-5, 7-9, 11-16, 22, 29 and 30 are rejected.

Claims 1-5, 7-9, 11-16, 22, 29, 30 and 45 are objected to.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached 9:00 am - 5:30 pm EST (M-F).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey J. Stucker can be reached at (571) 272-0911. The

fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/G.E./

Gregory S. Emch
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24 April 2009

/Daniel E. Kolker/
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April 27, 2009